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KIDNEY CANCER

CCR4: a new target for RCC

The chemokine receptor CCR4 is expressed in the tumour microenvironments of several cancers and is associated with poor prognosis. New findings show that CCR4 is highly expressed in human renal cell carcinoma (RCC) and that blocking CCR4 with an anti-CCR4 antibody has anti-tumour activity in mice.

Frances Balkwill and her research group have always been interested in chemokine networks in cancer and in the way that chemokines can control the movement of cells in and out of a tumour microenvironment. "While profiling cancers for the most prominent chemokine receptors we unexpectedly found that CCR4 expression was high in some cancers, including RCC," she explains. "At the time we were also interested in the observation that CCR4 was present on both malignant cells and the leukocyte infiltrate."

> "The antibody reduced tumour burden by changing the phenotype of the myeloid cells"

Chiara Berlato *et al.* detected abundant CCR4 expression in biopsy samples from patients with advanced RCC, and a positive correlation between CCR4 positivity and immune infiltrates in the tumour core. To assess the effect of CCR4 inhibition, they administered the antagonistic anti-CCR4 antibody, Affi-5, to mice with RCC, which led to a reduction in tumour weight. Administration of Affi-5 did not reduce the proportion of infiltrating leukocytes in the tumour microenvironment but instead altered the phenotype of the immune infiltrate. "The antibody reduced tumour burden by changing the phenotype of the myeloid cells in the tumour microenvironment from potentially pro-tumour to anti-tumour," explains Balkwill. Blocking $CD4^+$ T-cell activity with a neutralizing antibody to MHCII inhibited the anti-tumour effects of Affi-5, indicating an essential role for $CD4^+$ T cells in mediating the effects of Affi-5 on tumour cells.

Balkwill and colleagues plan to extend their findings by assessing whether the effect of anti-CCR4 therapy can be enhanced by combining this approach with other immunotherapies. "We are also further investigating the role of CCR4 and its ligands on immune responses with the overall goal of developing a rationale for a clinical trial of anti-CCR4 therapy in renal and other CCR4-overexpressing cancers."

Susan J. Allison

ORIGINAL ARTICLE Berlato, C. *et al.* A CCR4 antagonist reverses the tumor-promoting microenvironment of renal cancer. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI82976 (2017)